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STAUROSPORINE ANALOGUES

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Abstract

Described are compounds of formula (I), wherein X is methylene, carbonyl or hydroxymethylene, R0 is oxygen or N-OR1; R1 is hydrogen, alkyl, cycloalkyl, aralkyl, acyl, SO2-Ra, or carboxyalkyl; Ra is lower alkyl, cycloalkyl; R2 is hydrogen, lower alkyl, cycloalkyl or acyl; R3 is hydrogen, halogen, amino, alcyl, alkyl, cycloalkyl, alkoxyalkyl or aralkyl; R4 and R5 independent of each other are hydrogen, hydroxy, nitro, amino, lower alkyl, cycloalkyl, lower alkoxy, carbamoyl or halogen; and R6 is hydrogen or nitro, excluding the compound wherein X is methylene, R0 is N-OH, R2 is methyl and R3, R4, R5 and R6 are hydrogen, and salts thereof, a process for the preparation of this type of compounds including staurosporin-4'-one oxime, pharmaceutical compositions comprising these compounds and the preparation thereof, and the use of these compounds and compositions for the theraputic treatment of the human or animal body.

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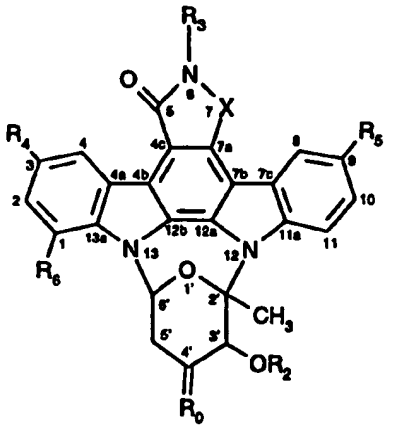

(I)

(57) Abstract

Described are compounds of formula (I), wherein X is methylene, carbonyl or hydroxymethylene, R_0 is oxygen or N-OR_1; R_1 is hydrogen, alkyl, cycloalkyl, aralkyl, acyl, SO_2-R_a, or carboxyalkyl; R_a is lower alkyl, cycloalkyl; R_2 is hydrogen, lower alkyl, cycloalkyl or acyl; R_3 is hydrogen, halogen, amino, alcyl, alkyl, cycloalkyl, alkoxyalkyl or aralkyl; R_4 and R_5 independent of each other are hydrogen, hydroxy, nitro, amino, lower alkyl, cycloalkyl, lower alkoxy, carbamoyl or halogen; and R_6 is hydrogen or nitro, excluding the compound wherein X is methylene, R_0 is N-OH, R_2 is methyl and R_3, R_4, R_5 and R_6 are hydrogen, and salts thereof, a process for the preparation of this type of compounds including staurosporin-4'-one oxime, pharmaceutical compositions comprising these compounds and the preparation thereof, and the use of these compounds and compositions for the theraputic treatment of the human or animal body.

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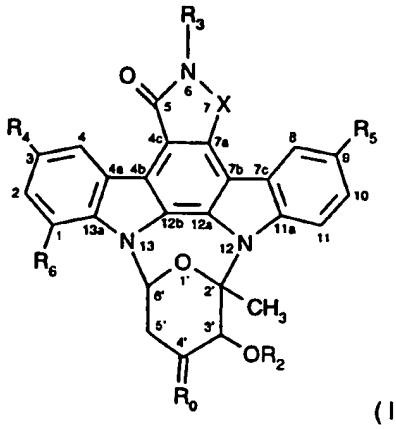
STAUROSPORINE ANALOGUES

The invention relates to compounds of formula I



(I),

wherein X is methylene, carbonyl or hydroxymethylene, R_0 is oxygen or N-OR_1, R_1 is hydrogen, alkyl, cycloalkyl, aralkyl, acyl, SO_2-R_a, or carboxyalkyl; R_a is lower alkyl or cycloalkyl, preferably C_1-C_3alkyl or cyclopropyl, most preferred methyl; R_2 is hydrogen, lower alkyl, cycloalkyl or acyl, R_3 is hydrogen, halogen, amino, acyl, alkyl, cycloalkyl, alkoxyalkyl or aralkyl, R_4 and R_5 independent of each other are hydrogen, hydroxy, nitro, amino, lower alkyl, cycloalkyl, lower alkoxy, carbamoyl or halogen, and R_6 is hydrogen or nitro, excluding the compound wherein X is methylene, R_0 is N-OH, R_2 is methyl and R_3, R_4, R_5 and R_6 are hydrogen, and salts thereof, to a process for the preparation of this type of compounds including staurosporin-4'-one oxime, to pharmaceutical compositions comprising these compounds and the preparation thereof, and to the use of these compounds and compositions for the therapeutic treatment of the human or animal body.

Here and in the following representatives of the formula I, wherein R_0 is oxygen are named ketones of the formula Ia and representatives wherein R_0 is N-OR_1 are named oximes of the formula Ib (c.f. the reaction scheme provided with the description of the preparation of theses compounds). The oxime that is excluded from the scope of formula I, namely that one, wherein X is methylene, R_0 is N-OH, R_2 is methyl and R_3, R_4, R_5 and R_6 are hydrogen is the staurosporin-4'-one oxime (TAN-1030A). It is described as a fermentation product by Tanida, S. *et al.*, in J. Antibiot. (1989) 42, 1619-1630. The advantage of the present invention is that this already known staurosporin-4'-one oxime as well as all other oximes of

the formula Ib_1 and Ib_2 and the ketones of the formula Ia can now be produced in high quantities by chemical means starting from commercially available compounds of the formula II or from compounds obtainable analogously to procedures described in the literature. Therefore, the chemical process for the preparation of these compounds which can be either used as active ingredients in pharmaceuticals or which represent valuable starting compounds for the preparation of novel active ingredients represents an essential part of the present invention.

Within the scope of this description, the definitions used hereinbefore and hereinafter have preferably the following meanings and, unless indicated to the contrary, organic radicals referred to as "lower" contain from one to seven, and preferably from one to four, carbon atoms and are unbranched or branched. For example, "lower alkyl" stands for C_1-C_7alkyl, preferably C_1-C_4alkyl, "lower alkoxy" represents C_1-C_7alkoxy, preferably C_1-C_4alkoxy. Cycloalkyl stands for a cyclic alkyl moiety including C_1-C_7cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Most preferred is cyclopropyl. Carboxyalkyl stands for a branched or unbranched alkyl moyety substituted by COOH, preferably for a branched or unbranched lower alkylmoyety substituted by COOH.
"Amino" stands for an amino group of the formula $-N(R_7)(R_8)$, wherein R_7 and R_8 independently of each other are hydrogen or C_1-C_6alkyl, preferably hydrogen or C_1-C_4alkyl, mostly preferred hydrogen.
"Halogen" stands for a halogen atom, preferably for chlorine or fluorine, but also for bromine or iodine.

Within the meaning of R_3 "acyl" is an acyl radical derived from a free or functionally modified carboxylic acid and is characterised especially by the partial formula Z-C(=W)-, wherein W is oxygen or sulfur and Z is hydrogen, hydrocarbyl, hydrocarbyloxy, an amino group, especially one of the formula $-N(R_7)(R_8)$, as definded above, or chlorine.

Hydrocarbyl Z in such an acyl radical has a total of preferably not more than 30, and especially not more than 19, carbon atoms and is an aliphatic hydrocarbon, aryl or heteroaryl radical, or also an araliphatic or heteroaraliphatic radical.

An aliphatic unsubstituted hydrocarbon radical Z is saturated or unsaturated. Unsaturated hydrocarbon radicals Z are those which contain one or more, especially conjugated and/or

non-conjugated multiple bonds (double and/or triple bonds). There is preferred as an aliphatic hydrocarbon radical Z a straight-chain or branched lower alkyl, lower alkenyl or lower alkynyl radical. Lower alkyl is e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl; lower alkenyl is e.g. allyl, propenyl or isopropenyl; lower alkynyl is e.g. propargyl or 2-butynyl. In corresponding unsaturated radicals, the double bond is preferably not situated in the α-position with respect to the free valency.

An aryl radical Z is a carbocyclic radical in which at least one ring is in the form of a 6-membered aromatic ring (i.e. a benzene ring). Preferred are phenyl, naphthyl, such as 1- or 2-naphthyl, biphenylyl, such as, especially, 4-biphenylyl, anthryl and fluorenyl and also such ring systems having one or more fused saturated rings.

An araliphatic radical Z is an aryl-substituted alkyl radical. Preferred are aryl-lower alkyl and aryl-lower alkenyl radicals, e.g. phenyl-lower alkyl or phenyl-lower alkenyl having a terminal phenyl radical, e.g. benzyl, 1- or 2-phenethyl, 1-, 2- or 3-phenylpropyl, diphenylmethyl (benzhydryl), trityl and cinnamyl, and also 1- or 2-naphthylmethyl.

The term "heteroaryl" embraces heterocyclic compounds of aromatic character, e.g. those in which at least one 5- or 6-membered heterocyclic ring contains the maximum number of non-cumulative double bonds.

A heteroaryl radical Z is especially a monocyclic, but also a bicyclic, aza-, thia-, oxa-, thiaza-, oxaza-, diaza-, triaza- or tetraza-cyclic radical of aromatic character the free valency of which must extend from one of its carbon atoms. More especially, it is a monocyclic radical containing one nitrogen, oxygen or sulfur atom, such as pyrrolyl, e.g. 2-pyrrolyl or 3-pyrrolyl, pyridyl, e.g. 2-, 3- or 4-pyridyl, thienyl, e.g. 2- or 3-thienyl, or furyl, e.g. 2-furyl; analogous bicyclic radicals containing one nitrogen, oxygen or sulfur atom are e.g. indolyl, such as 2- or 3-indolyl, quinolyl, such as 2- or 4-quinolyl, isoquinolyl, such as 3- or 5-isoquinolyl, benzofuranyl, such as 2-benzofuranyl, chromenyl, such as 3-chromenyl, or benzothienyl, such as 2- or 3-benzothienyl; preferred monocyclic and bicyclic radicals containing several hetero atoms are e.g. imidazolyl, such as 2-imidazolyl, pyrimidinyl, such as 2- or 4-pyrimidinyl, oxazolyl, such as 2-oxazolyl, isoxazolyl, such as 3-isoxazolyl, or thiazolyl, such as 2-thiazolyl, and benzimidazolyl, such as 2-benzimidazolyl, benzoxazolyl, such as 2-benzoxazolyl, or quinazolyl, such as 2-quinazolinyl, respectively.

Heteroaraliphatic radicals Z are preferably derived from aliphatic radicals having not more than 7, and preferably not more than 4, carbon atoms, e.g. those mentioned above, such as lower alkyl, especially methyl or ethyl, and may carry one, two or more heteroaryl radical(s), e.g. those mentioned above, it also being possible for the ring to be bonded to the aliphatic radical by a nitrogen atom.

Hydrocarbyl Z can be substituted by one, two or more identical or different substituents, especially by two or three substituents. Suitable substituents are especially the following: free, etherified and esterified hydroxy groups; mercapto, lower alkylthio and unsubstituted or substituted phenylthio groups; halogen atoms, such as chlorine and fluorine, but also bromine and iodine; oxo groups that are also in the form of corresponding acetals or ketals; azido and nitro groups; primary, secondary and, preferably, tertiary amino groups, primary or secondary amino groups protected by conventional protecting groups, acylamino groups and diacylamino groups, and free or functionally modified sulfo groups, such as sulfamoyl groups or sulfo groups in salt form. Preferably, the functional groups are not situated at the carbon atom from which the free valency extends but are separated therefrom by two or even more carbon atoms. The hydrocarbyl radical can also be substituted by free and functionally modified carboxy groups, such as carboxy groups in salt form or esterified carboxy groups, by carbamoyl, ureido or guanidino groups each unsubstituted or carrying one or two hydrocarbon radicals, such as lower alkyl, and by cyano groups. Other substituents of aryl or heteroaryl radicals Z are, for example, lower alkyl, such as methyl, ethyl, n-propyl, n-butyl and isobutyl, and halo-substituted lower alkyl, e.g. trifluoromethyl.

An etherified hydroxy group present as a substituent in the hydrocarbyl radical Z is e.g. a lower alkoxy group, such as a methoxy, ethoxy, propoxy, isopropoxy, butoxy or tert-butoxy group, which may also be substituted. For example, such a lower alkoxy group may be substituted by halogen atoms, e.g. by one, two or more halogen atoms, especially in the 2-position, such as in the 2,2,2-trichloroethoxy, 2-chloroethoxy or 2-iodoethoxy radical, or by hydroxy or lower alkoxy radicals, preferably by one in each case, especially in the 2-position, such as in the 2-methoxyethoxy radical. An especially preferred form of etherified hydroxy group is an oxaalkyl radical, in which, in a preferably linear alkyl, one or more carbon atoms are replaced by oxygen atoms which are preferably separated from one another by several (especially 2) carbon atoms so that they form a group $Y\text{-}(O\text{-}CH_2CH_2\text{-})_n$- wherein n= 1 to 14 and Y is hydrogen or lower alkyl, such as methyl or ethyl. Such

etherified hydroxy groups are also unsubstituted or substituted phenoxy radicals and phenyl-lower alkoxy radicals, such as especially benzyloxy, benzhydryloxy and triphenylmethoxy (trityloxy), and heterocyclyloxy radicals, such as especially 2-tetrahydropyranyloxy. A special etherified hydroxy group is the grouping methylenedioxy or ethylenedioxy; the former as a rule bridges 2 adjacent carbon atoms, especially in aryl radicals, and the latter is bonded to one and the same carbon atom and is to be regarded as a protecting group for oxo. Etherified hydroxy groups are also to be understood in this context as including silylated hydroxy groups, such as, for example, in tri-lower alkylsilyloxy, such as trimethylsilyloxy and dimethyl-tert-butylsilyloxy, or phenyl-di-lower alkylsilyloxy or lower alkyldiphenylsilyloxy.

An esterified hydroxy group present as a substituent in the hydrocarbyl radical Z carries an acyl radical characterised above, especially an acyl radical having not more than 12 carbon atoms, or is lactonised by a carboxy group also present in the hydrocarbyl radical Z.

An esterified carboxy group present as a substituent in the hydrocarbyl radical Z is one in which the hydrogen atom has been replaced by one of the hydrocarbon radicals characterised above, especially by a lower alkyl or phenyl-lower alkyl radical; as examples of an esterified carboxy group there may be mentioned lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl which is unsubstituted or substituted in the phenyl moiety, especially the methoxy-, ethoxy-, tert-butoxy- or benzyloxy-carbonyl group, and also a lactonised carboxy group.

A primary amino group $-NH_2$ as a substituent of the hydrocarbyl radical Z may also be in protected form as an acylamino group corresponding to that amino group. A secondary amino group carries instead of one of the two hydrogen atoms a hydrocarbyl radical, preferably an unsubstituted hydrocarbyl radical, such as one of those mentioned above, especially lower alkyl, and may also be in a protected form as an acylamino group derived therefrom and having a monovalent acyl radical characterised hereinbelow. It is characteristic of protecting groups that they can be removed readily, i.e. without undesired side-reactions taking place, for example by solvolysis, reduction, photolysis or under physiological conditions. Amino-protecting groups and their introduction and removal are known per se and described, for example, in T.W. Greene "Protective Groups in Organic Syntheses", Wiley, New York 1984.

An acyl radical serving as an amino-protecting group is preferably derived from a carbonic acid semi-derivative and is preferably lower alkoxycarbonyl or aryl-lower alkoxycarbonyl each of which is unsubstituted or substituted, especially by lower alkyl, lower alkoxy, nitro and/or by halogen, such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, 2,2,2--trichloroethoxycarbonyl, 2-iodoethoxycarbonyl, lower alkenyloxycarbonyl, e.g. allyloxy-carbonyl, benzyloxycarbonyl, 4-nitro- or 4-methoxy-benzyloxycarbonyl, 2-phenyl-2-propoxy-carbonyl, 2-p-tolyl-2-propoxycarbonyl, 2-(p-biphenylyl)-2-propoxycarbonyl or 9-fluor-enyl-methoxycarbonyl.

A tertiary amino group occurring as a substituent in the hydrocarbyl radical Z carries two different or, preferably, identical hydrocarbyl radicals (including the heteroaryl radicals), such as the unsubstituted hydrocarbyl radicals characterised above, especially lower alkyl.

A preferred amino group as a substituent of a hydrocarbyl radical Z is one of the formula $N(R_7)(R_8)$, wherein each of R_7 and R_8 independently of the other is hydrogen, unsubstituted aliphatic C_1-C_7hydrocarbyl, such as, especially, C_1-C_4alkyl or C_1-C_4alkenyl, or monocyclic unsubstituted or C_1-C_4alkyl-, C_1-C_4alkoxy-, halo- and/or nitro-substituted aryl, aralkyl or aralkenyl having not more than 10 carbon atoms, it being possible for carbon-containing radicals R_7 and R_8 to be bonded to each other by a carbon-carbon bond or by an oxygen atom, by a sulfur atom or by a nitrogen atom which is unsubstituted or substituted by hydrocarbyl, such as lower alkyl. In such a case, they form together with the nitrogen atom of the amino group a nitrogen-containing heterocyclic ring.

The following may be mentioned as examples of especially preferred amino groups: lower alkylamino, such as methylamino or ethylamino, di-lower alkylamino, such as dimethylamino or diethylamino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or 4-methylpiperazino, or phenylamino, diphenylamino, benzylamino and dibenzylamino each unsubstituted or substituted, especially in the phenyl moiety, e.g. by lower alkyl, lower alkoxy, halogen and/or by nitro; protected amino groups are preferably in the form of lower alkoxycarbonylamino, e.g. tert-butoxycarbonylamino, phenyl-lower alkoxycarbonylamino, e.g. 4-methoxybenzyloxycarbonylamino, and 9-fluorenylmethoxycarbonylamino.

In an acyl of the formula Z-C(=W)- wherein Z is an aliphatic hydrocarbon radical characterised above, the latter may carry especially from one to three substituents selected from the following: a carboxy group, which may also be in salt form or in the form of a cyano group or a C_1-C_4alkyl ester (C_1-C_4alkoxycarbonyl group) and which is preferably in the ω-position, an amino group of the formula -N(R_7)(R_8), defined above, preferably one in which each of R_7 and R_8 is hydrogen and which is then preferably in the 1-position, or one or more halogen atoms, especially fluorine or chlorine, which are preferably situated in the vicinity of the carbonyl group.

A preferred acyl is a bicyclic or, especially, a monocyclic aroyl, especially benzoyl, which may also carry one or more of the following substituents: halogen atoms, especially chlorine or fluorine, nitro groups, C_1-C_4alkyl radicals, especially methyl, hydroxy groups and etherified hydroxy groups, especially C_1-C_4alkoxy, such as methoxy, phenoxy and methylenedioxy, and carboxy groups which may also be in salt form or in the form of a cyano group or a C_1-C_4alkyl ester (C_1-C_4alkoxycarbonyl). The aroyl radicals carry preferably not more than two and especially only one of such substituents. Also preferred are analogous heteroaroyl radicals Ac_0, especially those that are derived from pyridine, furan, thiophene and imidazole and the analogues thereof having a fused benzene ring (such as quinoline, isoquinoline, benzofuran, benzothiophene and benzimidazole) and that are unsubstituted or also substituted as indicated above. Other preferred acyl radicals are derived also from monocyclic aryl-alkyl or aryl-alkenyl, e.g. benzyl and styryl (i.e. phenacetyl and cinnamoyl). These, too, may be substituted in the manner indicated above. For example, corresponding acyl radicals Ac_0 are derived from the following carboxylic acids: aliphatic monocarboxylic acids having not more than 10 carbon atoms, such as lower alkanecarboxylic acids, e.g. propionic, butyric, isobutyric, valeric, isovaleric, caproic, trimethylacetic, oenanthic and diethylacetic acid and, especially, acetic acid, but also corresponding halogenated lower alkanecarboxylic acids, such as chloroacetic acid, trifluoroacetic acid or trichloroacetic acid, bromoacetic acid or α-bromoisovaleric acid, aromatic carbocyclic carboxylic acids, e.g. benzoic acid, which may be mono- or poly-substituted as indicated above; aryl- or aryloxy-lower alkanecarboxylic acids and analogues thereof that are unsaturated in the chain, e.g. phenylacetic or phenoxyacetic acids, phenylpropionic acids and cinnamic acids each unsubstituted or substituted as indicated above for benzoic acid; and heteroaryl acids, e.g. furan-2-carboxylic acid, 5-tert-butylfuran-2-carboxylic acid, thiophene-2-carboxylic acid, nicotinic or isonicotinic acid, 4-pyridine-

propionic acid, and pyrrole-2- or -3-carboxylic acids which are unsubstituted or substituted by lower alkyl radicals; also corresponding α-amino acids, especially naturally occurring α-amino acids, e.g. glycine and the α-amino acids of the L series, such as phenylglycine, alanine, phenylalanine, proline, leucine, isoleucine, serine, threonine, valine, tyrosine, arginine, histidine, lysine, aspartic acid, glutamic acid, glutamine and asparagine, preferably in an N-protected form, i.e. in a form in which the amino group is substituted by a conventional amino-protecting group, e.g. one of those mentioned above, and also dicarboxylic acids, such as oxalic acid, malonic acid, mono- or di-lower alkylmalonic acids, succinic acid, glutaric acid, adipic acid, maleic acid, or phthalic acid which is unsubstituted or substituted by halogen, such as fluorine, chlorine or bromine, lower alkyl, hydroxy, lower alkoxy and/or by nitro. As mentioned, the second carboxy group not only may be free but also may be functionally modified, for example may be present in the form of a C_1-C_4alkyl ester group or in the form of a salt.
Hydrocarbyl in a hydrocarbyloxy radical Z has the same general and preferred meanings as those indicated above.

A corresponding preferred acyl is derived from monoesters of carbonic acid (hydrocarbyl-oxycarbonyl). This acyl accordingly forms with the basic structure of the compounds of formula I corresponding N-disubstituted urethanes. Among especially preferred hydrocarbyl radicals in those derivatives there may be mentioned, for example, the following: aliphatic hydrocarbyl, especially a C_1-C_{20}alkyl, preferably a linear C_1-C_{20} alkyl, that may be substituted by a carboxy group which is preferably in a functionally modified form, such as in the form of a salt, cyano or a C_1-C_4alkyl ester, and is preferably situated in the ω-position, a branched lower alkyl, e.g. tert-butyl, or unsubstituted or substituted phenyl and benzyl radicals, e.g. those mentioned above as being preferred.

Another preferred acyl group is derived from amides of carbonic acid (or also thiocarbonic acid) and is characterised by the formula $(R_7)(R_8)N$-C(=W)-, wherein R_7 and R_8 are as defined above and W is sulfur or, especially, oxygen. This acyl radical accordingly forms with the basic structure of the compounds of formula I corresponding ureas or thioureas. Among preferred compounds according to the invention that carry this acyl, prominence is to be given especially to those wherein W is oxygen, one of the radicals R_7 and R_8 is hydrogen and the other is phenyl or C_1-C_7alkyl each of which may be substituted by

hydroxy, mercapto, methylthio, phenyl, p-hydroxyphenyl, p-methoxyphenyl and, especially, by carboxy (in free form or in a functionally modified form, such as C_1-C_4alkoxycarbonyl, carbamoyl or amidino). Prominence is also to be given to compounds wherein W is sulfur, one of the radicals R_7 and R_8 is hydrogen and the other is C_1-C_7alkyl or, especially, C_1-C_7-alkenyl in which the free valency extends from a carbon atom other than that from which the double bond extends, such as allyl.

Prominence is also to be given to the compounds of formula I according to the invention wherein X and R_2 are as defined above and R_1 is chloroformyl or thiochloroformyl, which compounds are distinguished especially by being advantageous intermediates for the preparation of modified carbonic acid acyl esters.

Especially preferred are acyl groups of the partial formula Z-C(=W)- wherein W is oxygen and Z is C_1-C_7alkyl, especially C_1-C_4alkyl, such as methyl, propyl or tert-butyl, which may also be substituted by halogen, such as fluorine or chlorine, carboxy or by C_1-C_4 alkoxy-carbonyl, such as methoxycarbonyl, such as trifluoromethyl or trichloromethyl, 2-carboxy- or 2-methoxycarbonyl-ethyl, or phenyl or benzyl each of which may be unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, such as fluorine or chlorine, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano.

Especially preferred as the radical R_1 is a C_1-C_7alkoxycarbonyl, especially a C_1-C_4alkoxy carbonyl, radical or a phenyloxycarbonyl radical which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano.

Especially preferred are acyl radicals of the partial formula $(R_7)(R_8)$N-C(=W)-, wherein W is sulfur or, especially, oxygen, R_7 is hydrogen and R_8 is C_1-C_7alkyl, especially C_1-C_4alkyl, or phenyl each of which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano.

Especially preferred as the radical R_1 are acyl radicals that are derived from an α-amino acid, especially a naturally occurring α-amino acid of the L series.

Especially preferred are acyl radicals that are derived from an α-amino acid selected from glycine, phenylglycine, alanine, phenylalanine, proline, leucine, isoleucine, serine, threonine, valine, tyrosine, arginine, histidine, lysine, glutamine, glutamic acid, aspartic acid and asparagine.

Especially preferred are those acyl radicals R_1 that are derived from an α-amino acid in which the α-amino group is protected by an amino-protecting group, e.g. tert-butoxy-carbonyl.

Alkyl R_1 is an unsubstituted or substituted radical that has a total of not more than 19 carbon atoms, especially a straight-chain or branched lower alkyl radical. Lower alkyl is e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl or tert.-butyl. Alkyl R_1 can be substituted by one, two or more identical or different substituents, e.g. those mentioned above for hydrocarbyl. Preferred alkyl radicals R_1 are C_1-C_7alkyl, C_2-C_7hydroxyalkyl in which the hydroxy group is in any position other than the 1-position and is preferably in the 2-position, cyano-[C_1-C_7]alkyl in which the cyano group is preferably in the 1- or the ω-position, or carboxy-[C_1-C_7]alkyl in which the carboxy group is preferably in the 1- or the ω-posi tion and may also be in salt form or in the form of a C_1-C_4alkyl ester (C_1-C_4alkoxycarbonyl) or benzyl ester (benzyloxycarbonyl).

A functionally modified carboxy group R_2 preferably means that the carboxy group may also be in the form of esterified carboxy that can be cleaved under physiological conditions or in the form of cyano, or that the hydroxyl radical of the carboxy group has been replaced by amino (carbamoyl) or the hydrogen atom of the carboxy group has been replaced by alkyl (alkoxycarbonyl).

Esterified carboxy groups R_2 that can be cleaved under physiological conditions (i.e. metabolisable esterified carboxy groups R_2) are known from the chemistry of antibiotics. Suitable groups are especially acyloxymethoxycarbonyl groups wherein acyl is, for example, the radical of an organic carboxylic acid, especially an unsubstituted or substituted lower alkanecarboxylic acid, or wherein acyloxymethyl forms the radical of a lactone. Such groups are e.g. lower alkanoyloxymethoxycarbonyl, e.g. acetoxymethoxycarbonyl or pivaloyloxy-methoxycarbonyl, amino-lower alkanoyloxymethoxycarbonyl, especially α-amino-lower

alkanoyloxymethoxycarbonyl, and 4-crotonolactonyl. Other esterified carboxy groups R_2 that can be cleaved under physiological conditions are e.g. 5-indanyloxycarbonyl, phthalidyloxy-carbonyl, 1-lower alkoxycarbonyloxy-lower alkoxycarbonyl, 1-lower alkoxy-lower alkoxycarbonyl, e.g. 1-ethoxycarbonyloxyethoxycarbonyl or also 2-oxo-1,3-dioxolan-4-yl-methoxycarbonyl that in the 5-position of the dioxolene ring is unsubstituted or is substituted by lower alkyl or by phenyl.

In an alkoxycarbonyl group R_2 alkyl has the same general and preferred meanings as those given above.

Preferred as the radical R_2 is carboxy or functionally modified carboxy that is in the form of an alkoxycarbonyl group, especially a lower alkoxycarbonyl group, for example ethoxy-carbonyl and, especially, methoxycarbonyl.

The invention relates especially to compounds of formula I wherein X is methylene or carbonyl, R_1 is hydrogen, acyl of the partial formula Z-C(=W)-, wherein W is oxygen or sulfur and Z is C_1-C_7alkyl, especially C_1-C_4alkyl, such as methyl, propyl or tert-butyl, which may be unsubstituted or substituted by phenyl, phenyloxy, amino, halogen, such as fluorine or chlorine, carboxy, cyano and/or by C_1-C_4alkoxycarbonyl, such as methoxycarbonyl, such as aminomethyl, 2-aminoethyl, trifluoro- or trichloro-methyl, 2-carboxy- or 2-methoxy-carbonyl-ethyl, or 3-carboxypropyl, phenyl which is unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4alkoxy, halogen, such as fluorine or chlorine, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano, C_1-C_{20}alkoxy, especially tert-butoxy, phenyloxy or benzyloxy each of which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4-alkoxy, halogen, such as fluorine or chlorine, nitro, trifluoromethyl, carboxy, C_1-C_4 alkoxy-carbonyl, methylenedioxy and/or by cyano, acyl of the partial formula $(R_7)(R_8)N$-C(=W)-, wherein W is sulfur or, especially, oxygen, R_7 is hydrogen and R_8 is C_1-C_7alkyl, especially C_1-C_4alkyl, or phenyl each of which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4-alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano, or is an acyl radical derived from an α-amino acid, especially an acyl radical derived from glycine, phenylglycine, alanine, phenylalanine, proline, leucine, isoleucine, serine, threonine, valine, tyrosine, arginine, histidine, lysine, glutamine, glutamic acid, aspartic acid or asparagine, in which the α-amino group is free or protected by an amino-protecting group and it being possible, in corresponding amino acids having an additional

carboxy group, for the carboxy group also to be esterified, or wherein R_1 is C_1-C_7alkyl, C_2-C_7 -hydroxyalkyl in which the hydroxy group is in any position other than the 1-position and is preferably in the 2-position, cyano-[C_1-C_7]alkyl in which the cyano group is preferably in the 1- or the ω-position or carboxy-[C_1-C_7]alkyl in which the carboxy group is preferably in the 1- or the ω-position and may also be in salt form or in the form of a C_1-C_4alkyl ester (C_1-C_4-alkoxycarbonyl) or a benzyl ester (benzyloxycarbonyl), R_2 is carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, cyano or esterified carboxy that can be cleaved under physiological conditions, and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

The invention relates chiefly to compounds of formula I wherein X is methylene, carbonyl or hydroxymethylene, R_1 is hydrogen, acyl of the partial formula Z-C(=O)-, wherein Z is C_1-C_7 alkyl, such as methyl, ethyl or n-propyl, which is unsubstituted or substituted by phenyl, phenyloxy, halogen, such as fluorine or chlorine, carboxy and/or by C_1-C_4alkoxycarbonyl, such as methoxycarbonyl or ethoxycarbonyl, or phenyl, C_1-C_7alkoxy, such as methoxy, ethoxy, n-propoxy, isobutoxy or tert-butoxy, or phenyloxy each of which is unsubstituted or is substituted by halogen, such as fluorine or chlorine, carboxy, C_1-C_4alkoxycarbonyl, such as methoxycarbonyl, C_1-C_4alkoxy, such as methoxy, C_1-C_4alkyl, such as methyl, and/or by nitro, or the acyl radical of a naturally occurring α-amino acid, such as glycine, alanine, serine or phenylalanine, in which the amino group may be protected by an amino-protecting group, such as lower alkoxycarbonyl, e.g. tert-butoxycarbonyl, or wherein R_1 is C_1-C_4alkyl, cyano-C_1-C_4alkyl, such as cyanoethyl, carboxy-C_1-C_4alkyl, such as carboxymethyl, R_2 is carboxy or lower alkoxycarbonyl, and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

The invention relates more especially to compounds of formula I wherein X is methylene, carbonyl or hydroxymethylene, R_1 is hydrogen, benzoyl, C_1-C_4alkoxycarbonyl, such as tert-butoxycarbonyl, or glycyl or L-alanyl in each of which the amino group may be protected by C_1-C_4alkoxycarbonyl, R_2 is carboxy or C_1-C_4alkoxycarbonyl, and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

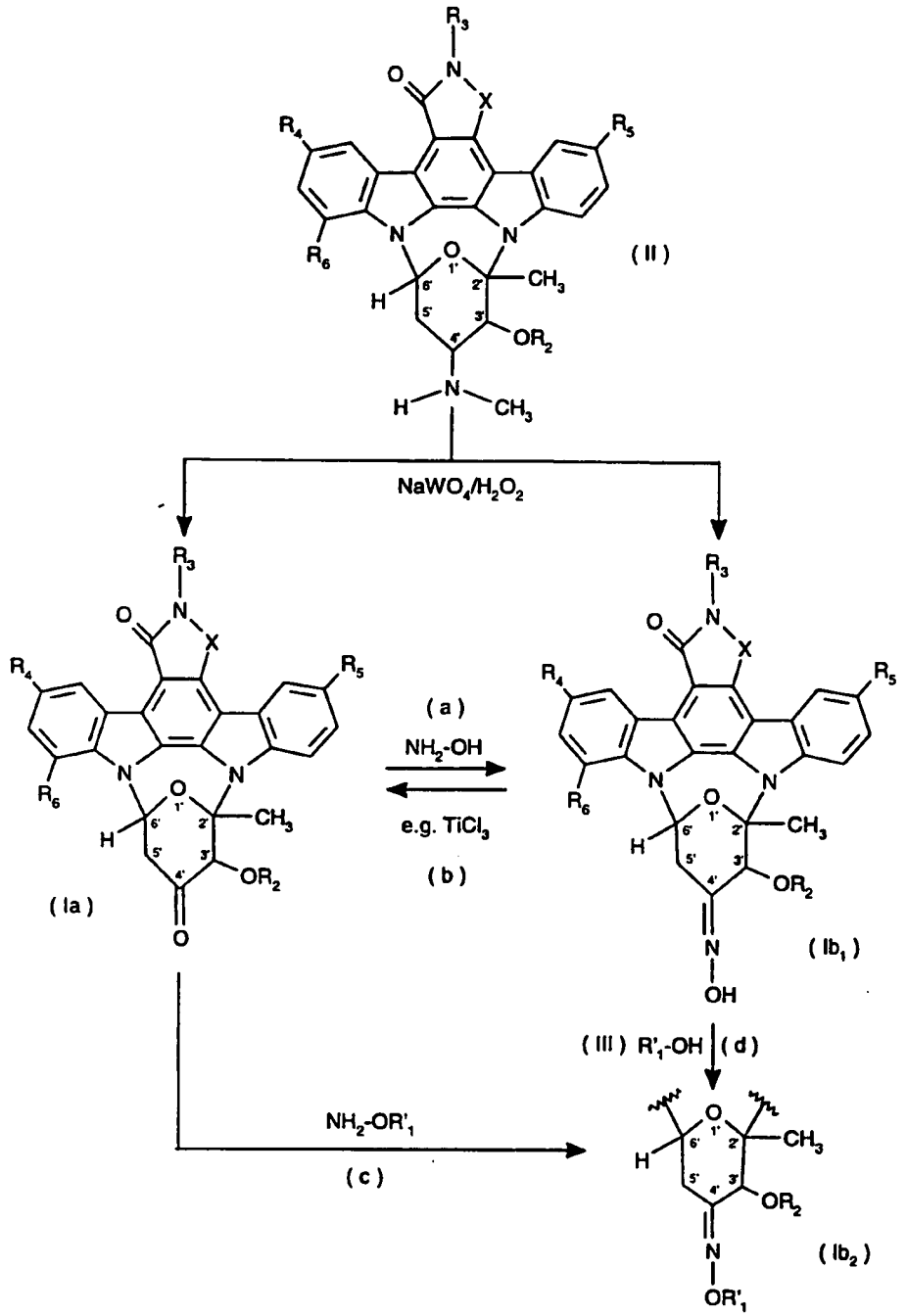
Especially preferred are compounds of the formula I, wherein R_3, R_4, R_5, and R_6 are hydrogen, and X, R_0 and R_2 are defined as under formula I or as in any one of the preceding subgroups; or a salt thereof.

A further especially preferred subgroup consists of compounds of the formula I, wherein X stands for methylen, R_3, R_4, R_5, and R_6 are hydrogen, and R_0 and R_2 are defined as under formula I or as in any one of the preceding subgroups; or a salt thereof.

Another especially preferred subgroup consists of compounds of the formula I, wherein X stands for carbonyl, R_3, R_4, R_5, and R_6 are hydrogen, and R_0 and R_2 are defined as under formula I or as in any one of the preceding subgroups; or a salt thereof.

The invention relates most especially to the compounds of formula I described in the examples and their salts.

A compound of the formula I wherein X is methylene, carbonyl or hydroxymethylene, R_0 is oxygen or N-OR_1, R_1 is hydrogen, alkyl, cycloalkyl, aralkyl, acyl, SO_2-R_a, or carboxyalkyl; R_a is lower alkyl or cycloalkyl, preferably cyclopropyl or C_1-C_3alkyl, most preferred methyl; R_2 is hydrogen, lower alkyl, cycloalkyl or acyl, R_3 is hydrogen, halogen, amino, acyl, alkyl, cycloalkyl, alkoxyalkyl or aralkyl, R_4 and R_5 independent of each other are hydrogen, hydroxy, nitro, amino, lower alkyl, cycloalkyl, lower alkoxy, carbamoyl or halogen, and R_6 is hydrogen or nitro, and salts thereof, can be prepared by a novel process in accordance with the following reaction scheme



wherein the substituents X, R_2, R_3, R_4, R_5 and R_6 are defined as above and R'_1 is one of the radicals R_1 with the exception of hydrogen,

which process comprises

oxidising a compound of the formula II with a suitable oxidising agent, e.g. $NaWO_4/H_2O_2$, to result in a mixture of a ketone of the formula Ia and an oxime of the formula Ib_1, isolating the mixture and separating the keton Ia from the oxime Ib_1 and

(a) optionally derivatizing the ketone Ia with a suitable derivatizing agent, e.g. NH_2-OH, to form the oxime Ib_1 or

(b) optionally hydrolyzing the oxime Ib_1 with a suitable hydrolyzing agent, e.g. $TiCl_3$, to form a ketone Ia or

(c) optionally derivatizing the ketone Ia with a derivatizing agent NH_2-OR'_1, wherein R'_1 is one of the radicals R_1 with the exception of hydrogen, to form the oxime Ib_2, wherein R'_1 has the same meanings or

(d) optionally derivatizing the oxime Ib_1 with a suitable alkylation or acylation reagent R'_1 - OH, to form the oxime Ib_2, wherein R'_1 is alkyl, cycloalkyl, aralkyl, acyl, SO_2-R_a, or carboxyalkyl and R_a is lower alkyl or cycloalkyl,

(e) optionally derivatizing R_2 standing for hydrogen with an alkylating or acylating agent, and converting a compound of formula Ia, Ib_1 or Ib_2 obtained in free form into a salt thereof or a compound of formula Ia, Ib_1 or Ib_2 obtained in the form of a salt into its free form or into a different salt.

The reaction as outlined in the above reaction scheme leads in the first instance to a mixture of ketones of the formula Ia and oximes of the formula Ib_1 and Ib_2 respectively. Both types of compounds - ketones and oximes - and their pharmaceutically acceptable salts can be used e.g. as medicaments. Due to the reactive group in 4' position - keto group in Ia and the oxime group in Ib_1 and Ib_2 - the compounds of the formula Ia, Ib_1 and Ib_2 represent valuable starting compounds for the production of novel derivatives that can be used as active ingredients in pharmaceuticals. R_2 is typically hydrogen or methyl.

As mentioned initially, the advantage of the present invention is that the already known staurosporin-4'-one oxime as well as the ketones of the formula Ia and the oximes of the formula Ib_1 or Ib_2 can now be produced in high quantities by chemical means starting from commercially available compounds of the formula II or from compounds obtainable analogously to procedures described in the literature.

A ketone of the formula Ia can be derivatized in accordance with reaction step (a) with a suitable derivatizing agent, e.g. hydroxylamine, to form an oxime Ib_1 or in accordance with

reaction step (c) with a substituted hydroxylamine NH_2-OR'$_1$, wherein R'$_1$ is alkyl, cycloalkyl, aralkyl, acyl, SO_2-R_a, or carboxyalkyl and R_a is lower alkyl or cycloalkyl, to form an oxime Ib_2, wherein R'$_1$ is alkyl, cycloalkyl, aralkyl, acyl, SO_2-R_a, or carboxyalkyl and R_a is lower alkyl or cycloalkyl. Hydroxylamine and substituted hydroxylamine NH_2-OR'$_1$ are customarily used chemicals and derivatizations of this type are widely described in the literature.

An oxime Ib_1 can be hydrolyzed in accordance with reaction step (b) with a suitable hydrolyzing agent, e.g. $TiCl_3$, zinc /molybden(V)chloride or Zn / diluted acetic acid, to form a ketone Ia. Methods for the hydrolysis of oxims are generally known and, for example, described in Houben-Weyl, Vol X/4 p 269 ff. and include hydrolysis (e.g. diluted sufuric acid) or replacement by a more reactive ketone, e.g. 2,4-pentadione. Oxidative clavage is achieved by nitrous acid an other reagents and reductive clavage by $TiCl_3$, zinc /molybden(V)chloride or Zn / diluted acetic acid.

An oxime Ib_1 can be derivatized in accordance with reaction step (d) with a suitable alkylation or acylation reagent of the formula III

R'$_1$ - OH (III),

wherein R'$_1$ is one of the radicals R_1 with the exception of hydrogen, or preferably with a reactive derivative thereof having the formula IIIa

R'$_1$ - T (IIIa),

wherein R'$_1$ is one of the radicals R_1 with the exception of hydrogen and T is a reactively activated hydroxy.

This derivatization represents an alkylation or acylation of the hydroxygroup of the oxime Ib_1 an can be carried out in customary manner. This type of reaction is widely described in the literature, for example in Houben-Weyl Vol. 10/1, pp 1181 to 1238 and Houben-Weyl Vol. E16/a1 pp 214 to 270.

For example, for introducing into an oxime Ib_1 a substituent R_1 having the meaning alkyl, cycloalkyl or aralkyl one can use, for example, the corresponding alcohol or a reactive ester thereof. Suitable reactive esters of the desired alcohols are, for example, those with strong inorganic or organic acids, such as corresponding halides, sulfates, lower alkanesulfonates or substituted or unsubstituted benzenesulfonates, for example, chlorides, bromides, iodides, methane-, benzene- or p-toluolsulfonates. The etherification can be carried out, for

example, in the presence of a base, an alkali metall hydride, hydroxide or carbonate, or of an amine and in a temperature range from about -20°C to about 100 °C.

Oximes of the formula Ib_1 wherein R_1 is SO_2-R_a and R_a has the meanings given above can be prepared by reacting in customary manner the free oxime Ib_1 with the corresponding sulfonyl halide, preferably with the corresponding sulfonyl chloride or bromide. This reaction can be performed under the same conditions as described above for the etherification.

The acylation of the hydroxy group is effected, for example, in a manner known per se using a free acid of formula III as defined above or a salt thereof wherein R_1' is acyl. A suitable reactive derivative is, for example, a carboxylic acid of formula IIIa

R_1'-T (IIIa)

wherein R_1' is acyl, and wherein T is reactively activated hydroxy (the compound of formula IIIa therefore contains, instead of a hydroxy function bonded to the carbonyl group, reactively activated hydroxy, preferably as defined below). The free carboxylic acid of formula III can be activated, especially also in situ, for example, by strong acids, such as a hydrohalic, sulfuric, sulfonic or carboxylic acid, or acidic ion exchangers, for example by hydrochloric, hydrobromic or hydriodic acid, sulfuric acid, an unsubstituted or substituted, for example halo-substituted, alkane carboxylic acid, or by an acid of formula III, preferably with an excess of the acid of formula III, if necessary with the binding of the resulting water of reaction by water- binding agents, with removal of the water of reaction by azeotropic distillation or with extractive esterification, by acid anhydrides, especially inorganic or more especially organic acid anhydrides, for example carboxylic acid anhydrides, such as lower alkane carboxylic acid anhydrides (with the exception of formic acid anhydride), for example acetic anhydride, or by suitable activating or coupling reagents of the type mentioned below. R_1'-T may especially also be a carboxylic acid azide (T = azido; obtainable, for example, by reaction of a corresponding acid ester via the corresponding hydrazide and treatment thereof with nitrous acid); a carboxylic acid halide (T = halogen, especially chlorine or bromine), especially an acid chloride or bromide, obtainable, for example, by reaction with organic acid halides, especially with oxalyl dihalides, such as oxalyl dichloride, with inorganic acid halides, for example with acid halides of phosphorus or sulfur, such as phosphorus trichloride, phosphorus tribromide, phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride, phosphorus oxybromide, thionyl chloride or thionyl bromide, or especially under mild conditions with tetra-lower alkyl- a-halo-enamines, for

example tetramethyl-a-halo-enamines, especially 1-chloro- N,N,2-trimethyl-1-propeneamine (preferably by reaction under an inert gas, such as nitrogen, in inert solvents, especially chlorinated hydrocarbons, such as methylene chloride or chloroform, or ethers, such as diethyl ether, dioxane or tetrahydrofuran, or mixtures thereof, at preferred temperatures of from -78 to 50°C, especially from -60 to 30°C, for example from -10°C to room temperature [cf. Devos, A., et al., J. C. S. Chem. Commun. 1979, 1180-1181, and Haveaux, B., et al., Org. Synth. 59, 26 (1980)], it being possible for the resulting acid halide, for example the acid chloride of formula IIIa wherein T is chlorine, also to be used further directly in situ, for example by reaction with the compound of formula I wherein R_1' is hydrogen and the remaining radicals are as defined, in the presence of tertiary nitrogen bases, such as pyridine or 4-dimethylaminopyridine (DMAP, which is preferably added in catalytic amounts) or both of those bases, at preferred temperatures of from -20 to 50°C, especially from 10°C to 40°C; an activated ester wherein T is the radical of an alcohol having electron-attracting substituents, especially cyanomethoxy or aryloxy wherein aryl is preferably phenyl or naphthyl that is mono- or poly-substituted by halogen, nitro and/or by cyano, for example nitrophenoxy, such as 4-nitrophenoxy or 2,4-dinitrophenoxy, or polyhalophenoxy, such as pentachloro phenoxy; or a symmetrical or, preferably, asymmetrical acid anhydride which can be obtained, for example, by the action of a salt, for example an alkali metal salt, of an acid of formula III or its reaction partner, preferably a lower alkanecarboxylic acid, such as acetic acid, such as the sodium or potassium salt, on a complementary acid halide, and especially, in the case of the reaction with a salt of a carboxylic acid of formula III, a carboxylic acid halide, for example chloride, such as acetyl chloride, and, in the case of the reaction of a carboxylic acid halide of formula IIIa wherein T is halogen, for example chlorine or bromine, with a salt of a lower alkanecarboxylic acid, especially sodium or potassium acetate. There may be used as activating and coupling reagents for activating carboxylic acids of formula III in situ also carbodiimides, for example N,N'-di-C_1-C_4alkyl- or N,N'-di-C_5-C_7cycloalkyl-carbodiimide, such as diisopropylcarbodiimide or N,N'- dicyclohexyl-carbodiimide, advantageously with the addition of an activating catalyst, such as N-hydroxy-succinimide or unsubstituted or substituted, for example halo-, C_1-C_7alkyl- or C_1-C_7 lkoxy-substituted, N-hydroxy-benzotriazole or N-hydroxy-5-norbornene- 2,3-dicarboxamide, C_1-C_4alkyl haloformate, for example isobutyl chloroformate, suitable carbonyl compounds, for example N,N-carbonyldiimidazole, suitable 1,2-oxazolium compounds, for example 2-ethyl-5-phenyl-1,2-oxazolium 3'-sulfonate or 2-tert-butyl- 5-methyl-isoxazolium perchlorate, suitable acylamino compounds, for example 2-ethoxy-1-ethoxycarbonyl-1,2-dihydro-

quinoline, or suitable phosphoryl cyanamides or azides, for example diethylphosphoryl cyanamide or diphenylphosphoryl azide, also tri phenylphosphine disulfide or 1- C_1-C_4alkyl--2-halopyridinium halides, for example 1-methyl-2-chloropyridinium iodide. The compound of formula IIIa can also be a corresponding lower alkylthio ester (T= lower alkylthio).

If two free carboxy groups are present in the compound of formula III it is also possible for an internal anhydride to be present as activated acid derivative.

T is preferably halogen, such as chlorine or bromine, and also acyloxy, for example lower alkanoyloxy, such as acetyloxy.

The reaction with an acid halide, such as an acid chloride, of formula IIIa (T=Cl) is carried out especially in an ether, such as dioxane, tetrahydrofuran, or a nitrile, such as acetonitrile, or mixtures thereof, in the presence or absence of pyridine and in the absence or, preferably, in the presence of tertiary nitrogen bases, such as 4-dimethylaminopyridine, ethyl diisopropylamine, triethylamine or mixtures of two or more of those bases, with or without a protective gas, such as argon, at temperatures of from 0° to 80°C or the reflux temperature, for example from room temperature to 50°C or the reflux temperature if that is lower than 50°C.

A compound of formula Ia, Ib_1 or Ib_2 obtained in free form can be converted into a salt thereof or a compound of formula Ia, Ib_1 or Ib_2 obtained in the form of a salt can be converted into its free form or into a different salt.

The preparation of compounds of the formula Ia and Ib_1 or Ib_2 can be carried out either by starting from compounds of the formula II wherein X is either methylene, carbonyl or hydroxymethylene and R_2, R_3, R_4, R_5 and R_6 are either hydrogen or R_2, R_3, R_4, R_5 and R_6 have the other meanings given under formula I. In the first case the resulting compounds of the formula Ia, Ib_1 and Ib_2 are unsubstituted and the substituents can be introduced afterwards. In the second case the resulting compounds of the formula Ia, Ib_1 and Ib_2 are already substituted and no further substitution is necessary. It goes without saying that the reactivity of all reactive groups has to be taken into account whenever a substituent R_1, R_2, R_3, R_4, R_5 or R_6 is introduced into the molecule. Thus, functional groups in starting materials that are not to participate in the reaction, especially carbonyl and hydroxy groups, can be

protected by suitable protecting groups (conventional protecting groups) which are customarily used in the synthesis of organic compounds. Compounds of the formula I wherein R_2 is alkyl or cycloalkyl are advantageously produced from starting compounds of the formula II wherein the hydroxy group in position 3' is already alkylated.
The hydroxy group in position 3' can be etherified by methods known per se. The etherification can be carried out, for example, by using an alkohol or a reactive ester thereof. Suitable reactive esters of the desired alcohols are, for example, those with strong inorganic or organic acids, such as corresponding halides, sulfates, lower alkanesulfonates or substituted or unsubstituted benzenesulfonates, for example, chlorides, bromides, iodides, methane-, benzene- or p-toluolsulfonates. The etherification can be carried out, for example, in the presence of a base, an alkali metall hydride, hydroxide or carbonate, or of an amine and in a temperature range from about -20°C to about 100 °C.

For the acylation of the hydroxy group in position 3' (R_2 = acyl), the same procedure is applicable as described above for the replacement of R_1 = H by acyl. The acyl group can be introduced at each level, either at the level of the starting compounds of the formula II or at the level of the final compounds of the formula Ia, Ib_1 or Ib_2.

A compound of formula I wherein X is methylene, carbonyl or hydroxymethylene obtained in accordance with the present invention can, if desired, be converted into a different compound of formula I according to methods known *per se*.

For example, a compound of formula I wherein R_1 and R_2 are as defined under formula I and X is methylene can be converted with a suitable oxidising agent into a corresponding compound of formula I wherein X is carbonyl. The same applies to compounds of the formula II. Such an oxidising agent is one of the customary oxidising agents suitable for the oxidation of an activated methylene group, such as a benzyl group, to a carbonyl group, for example a compound of hexavalent chromium, such as an alkali metal chromate or dichromate, e.g. potassium chromate or potassium dichromate, and anhydrides of chromic acid, e.g. chromium trioxide, and complexes thereof, such as the chromium trioxide-pyridine complex, chromyl chloride or chromyl acetate, and esters of chromic acid, e.g. chromic acid tri-tert-butyl ester, a compound of quadrivalent to heptavalent manganese, e.g. manganese dioxide and potassium permanganate, ruthenium tetroxide and the like. Other suitable oxidising agents are peracids, their salts and hydroperoxides, e.g. potassium peroxodi-

sulfate, which are to be used in the presence of catalytic amounts of manganese(II) or manganese(III) salts, and, in a photooxidation, atmospheric oxygen in the presence of catalytic amounts of titanium(IV)oxide.

The oxidation is carried out in a manner known *per se* in an inert solvent, such as a protic solvent, such as water or glacial acetic acid (e.g. when using chromium trioxide or an oxidising salt), an aprotic solvent, such as benzene, pyridine, acetone, diethyl ether, carbon tetrachloride, methylene chloride, carbon disulfide and the like (e.g. when using chromyl chloride, chromium trioxide-pyridine complex etc.), or in mixtures of such solvents, and, when using two immiscible solvents, such as water and benzene, also in the presence of a phase-transfer catalyst, such as a quaternary ammonium compound, e.g. benzyltrimethyl-ammonium chloride, tetrabutylammonium chloride or cetyltrimethylammonium bromide, and, when using an oxidising salt, e.g. potassium permanganate, also in the presence of a crown ether, e.g. dicyclohexyl-18-crown-6, and, where appropriate, for example when using an oxidising salt, e.g. potassium dichromate, also in the presence of an equimolar amount of a strong inorganic acid, e.g. sulfuric acid, and, depending upon the nature of the oxidising agent used, at room temperature or at reduced or elevated temperature, e.g. in a temperature range of from approximately 0° to approximately 100°C. When using chromyl chloride or chromyl acetate as oxidising agent, the initially formed adduct must, when reaction is complete, be hydrolysed with water to form the desired compound of formula II.

Mixtures of diastereoisomeric compounds obtainable according to the process are separated by means of physico-chemical methods known *per se* into the individual diastereoisomers. Such methods include, for example, fractional crystallisation, liquid chromatography and adsorption chromatography.

The formation of salts and the freeing of the fundamental forms of the compounds of formula I from their salts, which may be carried out if desired, is effected in a conventional manner that is known *per se*. For example, compounds of formula I carrying carboxy are converted into corresponding salts, especially alkali metal salts, by treatment with a corresponding base, especially a compound giving an alkaline reaction, such as an alkali metal hydroxide, carbonate or hydrogen carbonate; the salts can be converted into free carboxy compounds by acidification, e.g. with inorganic acids, such as, especially, hydrohalic acids. Compounds of formula I containing primary, secondary or tertiary amino groups can be

converted into their salts with acids, e.g. by treatment with an acid suitable for forming salts, such as one of those mentioned above; conversely, by treatment with agents giving a basic reaction, such as with inorganic alkali metal hydroxides, carbonates and hydrogen carbonates, organic bases or ion-exchangers, such a basic fundamental form of an amine of formula I is freed.

Suitable compounds of the present invention may also form internal salts, e.g. by conventional titration to the neutral point or to the isoelectric point.
The latter or other salts of the novel compounds, e.g. the picrates, can also be used to purify the resulting compounds, by converting the free compounds into salts, separating the latter and recovering the free compounds from the salts again. In view of the close relationship between the compounds in free form and in the form of their salts, herein before and hereinafter any reference to the free compounds should be understood as including also the corresponding salts, as appropriate and expedient.

The invention relates also to those forms of the process according to which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out or a starting material is used in the form of a derivative, e.g. a salt, or is formed under the reaction conditions.

In the processes of the present invention, there are used starting materials that are known or that can be obtained by known methods, preferably those which result in the compounds described at the beginning as being especially valuable.

The reactions described above can be carried out under reaction conditions known *per se*, in the absence or, usually, in the presence of solvents or diluents, preferably those which are inert towards the reagents used and are solvents thereof, in the absence or presence of catalysts, condensation agents or neutralising agents, and, depending upon the nature of the reaction and/or the reactants, at reduced, normal or elevated temperature, e.g. in a temperature range of from approximately -80°C to approximately 190°C, preferably from approximately -20° to approximately 150°C, e.g. at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, e.g. under a nitrogen atmosphere.

The solvents from which the solvents suitable for any particular reaction can be selected include, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride, bis-lower alkane sulfines, such as dimethyl sulfoxide, acid amides, such as N,N-di-lower alkyl-lower alkanoylamides, for example dimethylformamide or dimethylacetamide, bases, such as heterocyclic nitrogen bases, for example pyridine, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless indicated to the contrary in the description of the processes. Other solvents specifically mentioned in individual process steps also belong to this list. Such solvents and solvent mixtures can also be used in working-up, for example by chromato graphy or partitioning.

The compounds according to the invention may also be in the form of salts, especially pharmaceutically acceptable, i.e. physiologically tolerable, salts. For isolation or purification it is also possible to use pharmaceutically unsuitable salts. Only pharmaceutically acceptable salts are used therapeutically and are preferred.

For example, compounds having free acid groups, for example a free sulfo or carboxy-group, especially one in the acyl radical Ac_0 or one that acts as the substituent R_2, may be in the form of salts, preferably physiologically tolerable salts, with a salt-forming basic component. Suitable salts are especially metal or ammonium salts, such as alkali metal and alkaline earth metal salts, e.g. sodium, potassium, magnesium or calcium salts, and ammonium salts with ammonia or suitable organic amines, especially tertiary mono amines and heterocyclic bases, e.g. triethylamine, tri-(2-hydroxyethyl)-amine, N-ethylpiperidine or N,N'-dimethylpiperazine. Such an acid group can also form an internal salt with the amino nitrogen of the staurosporin basic structure or with another amino group that may be present.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in protected form or in the form of a salt, or a compound obtainable in accordance with the process of the invention is produced under the process conditions and is processed further in situ. In the process of the present invention it is preferable to use those starting materials which result in the compounds described at the beginning as being especially valuable. Reaction conditions analogous to those mentioned in the examples are especially preferred.

Where necessary, protected starting compounds can be used at any stage of the process and the protecting groups can be removed at suitable stages of the reaction.

Compounds according to the invention of basic character may also be in the form of addition salts, especially in the form of acid addition salts with inorganic or organic acids. For example, compounds of formula I that carry in the radical R_1 or R_2 a basic group, such as an amino group, as substituent can form acid addition salts with common acids. Special prominence is to be given to addition salts that are formed by acid addition to the 9-amino group of the compounds of formula I, with physiologically tolerable salts being preferred.

The following common acids, for example, are suitable for salt formation: hydrohalic acids, e.g. hydrochloric and hydrobromic acid, sulfuric acid or phosphoric acid, and aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, fumaric, maleic, hydroxymaleic, oxalic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, anthranilic, p-hydroxybenzoic, salicylic, 4-aminosalicylic, embonic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenedisulfonic, halobenzenesulfonic, toluenesulfonic or sulfanilic acid, and also amino acids, such as methionine, tryptophan, lysine or arginine, and ascorbic acid.

Compounds of formula I may contain one or more chiral centres in their radicals. Accordingly, the invention relates to mixtures of diastereoisomers and especially to the novel diastereoisomers of compounds of formula I.

The starting compound of the formula II wherein X stands for methylene, R_2, is methyl and R_3, R_4, R_5 and R_6 are hydrogen is the antibiotic "staurosporine" which is a fermentation product produced by the strain *Streptomyces staurosporeus* [S. Omura et al. , J. Antibiot. 30, 275-281 (1977)]. Staurosporine is commercially available. Said *Streptomyces* strain was deposited with the Fermentation Research Institute, Japan, under the number FERM P-3725 in connection with the JP 57/53076, that was published on 11.11.82. Starting compounds of the formula II wherein X is methylene and R_2, R_3, R_4, R_5, and R_6 are hydrogen and their preparation is described in PCT publication WO 91/09034. Further compounds of the formula II wherein X is methylene or C=O, R_4, R_5 and R_6 are hydrogen and R_3 represents hydrogen, lower alkyl, formyl or amino are described in EP-0,383,919 which was published on 29.08.90. A compound of the formula II wherein X is a carbonyl group can also be prepared from the compound of the formula II wherein X stands for methylene by oxidation analogously to the oxidation described for compounds of formula I. In the same manner one can oxidise the methylene group X in the compound of the formula Ia or Ib in order to obtain their carbonyl analogues. The starting compounds of the formula II wherein X is hydroxymethylene can be prepared by reduction of a compound of the formula II wherein X is carbonyl. Such reduction reactions are widely described in the literature. The starting compounds of the formula II wherein X is hydroxymethylene can also be prepared analogously to the 7-hydroxymethylene staurosporine derivatives disclosed by G. Caravatti et al. in Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 3, pp. 399-404.

The starting compound of the formula II wherein R_3, R_4, R_5 and R_6 have other meanings than hydrogen can be obtained from their hydrogen analogues analogously to the reactions described in EP-0,303,697 and US-4,877,776 for the compound K-252 or KT-5556. Further reactions for introducing the substituents R_4 and R_5 are described in the Japanese patent application J0 3072-485 A or can be carried out in accordance with reactions used in organic chemistry for introducing substituents in aromatic ring systems.

The compounds of the formula I - which include the compounds of the formula Ia, Ib_1 and Ib_2 - of the present invention exert a pronounced inhibiting action on protein kinase C. Protein kinase C, which is dependent upon phospholipids and calcium, occurs in cells in several forms and participates in various fundamental processes, such as signal transmission, proliferation and differentiation, and in the release of hormones and neuro-

transmitters. These enzymes are known to be activated either by receptor-mediated hydrolysis of phospholipids of the cell membrane or by direct interaction with certain tumor-promoting substances. The sensitivity of a cell to receptor-mediated signal transmission is considerably influenced by the inhibition of the activity of protein kinase C (as the signal transmitter).

The protein kinase C inhibiting action is determined using protein kinase C from pigs' brains, which is purified by the procedure described by T.Uchida and C.R.Filburn in J.Biol. Chem. 259, 12311-4 (1984). The protein kinase C inhibiting action of the compounds of formula I is determined according to the method of D. Fabro *et al.*, Arch. Biochem. Biophys. 239, 102-111 (1985). In that test, the compounds of formula I inhibit protein kinase C at a concentration IC_{50} of as little as approximately from 0.01 to 0.2 µmol/litre.

The compounds of formula I also exhibit good inhibiting action (IC_{50} approximately from 0.005 to 0.2µmol/litre) on protein phosphorylase kinase. Other enzymes, e.g. EGF-R protein tyrosine kinase, on the other hand, are inhibited by the compounds of formula I only at a far higher, e.g. from 10 to 100 times higher, concentration.

Accordingly, the compounds of formula I and their pharmaceutically acceptable salts can be used e.g. as medicaments, especially for the treatment of tumour diseases. In addition, the compounds of formula I may possess anti-inflammatory, immuno-modulating, especially immunosuppressive, and antibacterial properties and can further be used as compositions against AIDS, arteriosclerosis and diseases of the cardiovascular system and the central nervous system.

The present invention further relates to the use of the compounds according to the invention for the preparation of medicaments, e.g. for the applications described above, for the therapeutic and prophylactic treatment of the human, and also the animal, body.

In view of the above-described pharmacological properties of the novel compounds, the present invention also includes the use of the active ingredients according to the invention on their own, where appropriate together with excipients, or in combination with other active ingredients, e.g. antibiotics or chemotherapeutic drugs, as compositions for the treatment of diseases in which, as described above, cell growth is of importance, both prophylactically

and curatively. When used as medicaments, the active ingredients according to the invention are administered in prophylactically or curatively effective amounts, preferably in the form of pharmaceutical compositions together with conven tional pharmaceutical carriers or excipients. There will be administered, for example, to a warm-blooded animal weighing approximately 70 kg, depending upon the species, body weight, age and individual condition, and depending upon the method of administration and especially also the particular syndrome, daily doses of approximately from 0.1 to 5000 mg, which, in acute cases, may be exceeded, especially from 50 mg to 5000 mg, preferably from 70 to 700 mg. The invention also includes accordingly the corresponding method of medical treatment.

The invention relates further to pharmaceutical compositions comprising the compounds of the present invention as active ingredients, and to processes for the preparation of those compositions.

The pharmaceutical compositions according to the invention are, for example, for enteral, such as peroral or rectal, and for parenteral administration to warm-blooded animals. Corresponding unit dose forms, especially for peroral administration, e.g. dragées, tablets or capsules, preferably comprise approximately from 5 to 500 mg, especially approximately from 10 to 100 mg, of active ingredient together with pharmaceutically acceptable carriers or excipients.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starch pastes (using, for example, corn, wheat, rice or potato starch), gelatin, gum tragacanth, methylcellulose and/or, if desired, disintegrators, such as the above-mentioned starches, also cyclodextrins, carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores can be provided with suitable coatings which may be enteric coatings, there being used, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycols and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments

may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Other orally administrable pharmaceutical compositions are dry-filled capsules consisting of gelatin, and also soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also be added.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. There may also be used gelatin rectal capsules that comprise a combination of the active ingredient with a base; suitable bases are, for example, liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

For parenteral administration there are suitable, especially, aqueous solutions of a form of the active ingredient that is soluble in water, e.g. a water-soluble salt, or aqueous injection suspensions comprising viscosity-increasing substances, for example sodium carboxy-methylcellulose, sorbitol and/or dextran, and, where appropriate, stabilisers. The active ingredient, where appropriate together with excipients, may also be in the form of a lyophilisate and may be dissolved by the addition of suitable solvents prior to parenteral administration.

The pharmaceutical compositions of the present invention are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture and processing the mixture or granules, if desired or necessary after the addition of suitable excipients, to form tablets or dragée cores.

The following Examples illustrate the invention described above, but do not imply any limitation of the scope thereof. Temperatures are given in degrees Celsius. The following abbreviations are used: TFA = trifluoroacetic acid, BOC= tert-butoxycarbonyl.

The following Examples 1 to 12 exemplify the prepration of 4'-demethylamino-staurosporine derivatives in accordance with the present invention.

Example 1 : 4'-demethylamino-4'-oxo staurosporine and the 4'-hydroximino analogue (TAN-1030A)

48 ml of a 30% hydrogen peroxide solution (47.0 mmole) is added to a stirred solution of 6.0 g of technical grade staurosporine (corresponding to 5.1 g of pure compound, 10.9 mmole) and 0.72 g (2.2 mmole) of sodium tungstate dihydrate in 140 ml of methanol and 140 ml of methylene chloride. The reaction mixture is stirred for 60 h at room temperature under protection from light. The reaction vessel is cooled in an ice bath and the excess of the hydrogen peroxide destroyed by the addition of a saturated solution of sodium bisulfite in 150 ml of water. The reaction mixture is diluted with an additional volume of 140 ml of methylene chloride. The clear biphasic mixture is separated. The aqueous phase is reextracted twice with 140 ml of methylene chloride. The combined organic solutions are washed with brine, dried over anhydrous sodium sulfate and evaporated to dryness on a rotatory evaporator. The residue of ca. 5 g is purified by column chromatography on silica gel (LiChroprep Si 60, MERCK, particle size 15-25 micron, column diameter 3.5 cm; length 50 cm). The fractions eluted with methylene chloride containing 1 % of 2-propanol are assayed by TLC. Homogenous fractions are pooled and evaporated to dryness providing 0.40 g (7 %) of 4'-demethylamino-4'-hydroximino-staurosporine and 1.2 g (24 %) of the 4'-oxo analogue. In addition 2.78 g (55 %) is recovered as a mixture of the two products. The 4'-oxo derivative is recrystallized from methylene chloride: white powder, m.p. 236-43°C. 4'-demethylamino-4' hydroximino staurosporine (TAN-1030A) is obtained in the form of almost colorless crystals from ethyl acetate/methanol, m.p. 238-44°C.

Example 2: 4'-demethylamino-4'-hydroximino staurosporine (TAN-1030A)

In a similar experiment as described in example 1, 5.0 g of technical grade staurosporine containing 84.7 % of pure compound (10.9 mmole) is dissolved in 120 ml of methanol and

120 ml of methylene chloride. After addition of 0.6 g (1.8 mmole) of sodium tungsten dihydrate and 4.0 ml of a 30 % hydrogen peroxide solution (39 mmole) the reaction mixture is stirred at room temperature for 60 h under protection from light. The reaction is then quenched by addition of 150 ml of saturated aquous sodium bisulfite solution under cooling. The work up is performed as described in example 1. The yellow oil obtained after evaporation of the solvent is redissolved in 80 ml of methanol and 80 ml of methylene chloride. Under stirring and cooling with an ice-bath 1.33 g (19.2 mmole) of hydroxylamine hydrochloride and 12 ml of pyridine are added to the suspension. The reaction mixture is stirred for 2 h at 0°C and subsequently diluted with water and an additional volume of methylene chloride. The aqueous layer is separated and extracted twice with 120 ml of methylene chloride containing 5 % of methanol. The organic phase is washed twice with water, dried over anhydrous sodium sulfate and concentrated in vacuo on a rotatory evaporator. The residue is recrystallized from methanol yielding 3.68 g (87.5 %) of pale yellow crystals which are analytically and spectroscopically indistinguishable from the 4'-demethylamino-4'-hydroximino staurosporine (TAN-1030A) obtained in example 1A.

Example 3: 4'-demethylamino-4'-oxo staurosporine

In a similar experiment as described in example 1 1.0 g of technical grade staurosporine containing 84.7 % of pure compound (2.18 mmol) is dissolved in 25 ml of methanol and 25 ml of methylene chloride. After addition of 0.12 g (0.36 mmol) of sodium tungsten dihydrate and 0.8 ml of a 30 % hydrogen peroxide solution (7.84 mmol) the reaction mixture is stirred at room temperature for 60 h under protection from light. The reaction is then quenched by the addition of a saturated solution of sodium bisulfite in 30 ml of water under cooling. The work up is performed as described in example 1. The yellow oil obtained after evaporation of the solvent is redissolved in 30 ml of dioxane and 2.0 g (26 mmol) ammonium acetate is added. 8 ml of 90% aqueous acetic acid are added as a solvent aid. The mixture is stirred under nitrogen and aqueous titanium trichloride (6.0 ml, 7 mmol) is added gradually. After 3.5 h the reaction mixture is diluted with 20 ml water and 40 ml CH_2Cl_2. The organic phase is washed with 40 ml portions each of 0.5 N sodium bicarbonate and water. The aqueous solutions are reextracted with 40 ml of methylene chloride. The combined organic solutions are dried by filtration through a silicone filter and concentrated *in vacuo*. The residue of ca. 0.70 g is purified by column chromatography on silica gel as described in example 1 to give 0.493g (51%) of 4'-demethylamino-4'-oxo staurosporine and 0.255 g (26%) of 4'-demethyl-amino-4' hydroximino staurosporine (TAN-1030A).

Example 4: 4'-demethylamino-4'-oxo staurosporine

To molybdenum(V)chloride (0.235 g, 0.86 mmol), water (110 µl) is added followed by tetrahydrofuran (6.4 ml). The mixture is stirred and zinc dust (56 mg, 0.86 mmol) and 4'-demethylamino-4'-hydroximino staurosporine (200 mg, 0.43 mmol) are added. After 4 h, the mixture is poured on 10 ml water and 10 ml CH_2Cl_2 and the biphasic mixture is separated. The aqueous phase is reextracted twice with 10 ml of methylene chloride. The combined organic phases - are dried over anhydrous sodium sulphate and the solvent removed *in vacuo*. The residue of ca. 0.18 g is purified by column chromatography on silica gel as described previously to give 0.104g (54%) of 4'-demethylamino-4'-oxo staurosporine and 0.021 g (11%) of starting material.

Example 5: O-methyl-4'-demethylamino-4'-hydroximino staurosporine

0.04 g (0.88 mmol) of 4'-demethylamino-4'-oxo staurosporine are dissolved in 20 ml of methanol and 20 ml of methylene chloride. Under stirring and cooling with an ice-bath 0.148 g of O-metylhydroxylamine hydrochloride and 3 ml of pyridine are added to the suspension. The reaction mixture is stirred for 2 h at 0°C and subsequently diluted with water and an additional volume of methylene chloride. The aqueous layer is separated and extracted twice with 20 ml of methylene chloride. The organic phase is washed twice with water, dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue is crystallized from diethyl ether yielding 0.404 g (95 %) of white crystals with MP of 196 - 200 °C.

Example 6: O-benzyl-4'-demethylamino-4'-hydroximino staurosporine

0.03 g (0.66 mmol) of 4'-demethylamino-4'-oxo staurosporine are dissolved in 15 ml of methanol and 15 ml of methylene chloride. Under stirring and cooling with an ice-bath 0.212 g (1.33 mmol) of O-benzylhydroxylamine hydrochloride and 3 ml of pyridine are added to the suspension. The reaction mixture is stirred for 4 h at 0°C and subsequently diluted with water and an additional volume of methylene chloride. The aqueous layer is separated and extracted twice with 20 ml of methylene chloride. The organic phase is washed twice with water, dried over anhydrous sodium sulphate and concentrated in vacuo on a rotatory evaporator. The residue is recrystallized from methanol/ethyl ether (1:8) yielding 0.342 g (92 %) of white crystals with MP of 287 - 290 °C.

Example 7: 3'-demethyl-4'-demethylamino-4' hydroximino staurosporine

5.0 g of technical grade 3'-demethyl staurosporine containing 88 % of pure compound (9.7 mmol) is dissolved in 120 ml of methanol and 120 ml of methylene chloride. After addition of 0.54 g (1.60 mmol) of sodium tungsten dihydrate and 3.5 ml of a 30 % hydrogen peroxide solution (35 mmol) the reaction mixture is stirred at room temperature for 60 h under protection from light. The reaction is then quenched by the addition of a saturated solution of sodium bisulfite in 150 ml of water under cooling. The reaction mixture is diluted with an additional volume of 140 ml of methylene chloride. The clear biphasic mixture is separated. The aqueous phase is reextracted twice with 140 ml of methylene chloride. The combined organic solutions are washed with brine, dried over anhydrous sodium sulphate and evaporated to dryness on a rotatory evaporator. The yellow oil obtained after evaporation of the solvent is redissolved in 80 ml of methanol and 80 ml of methylene chloride. Under stirring and cooling with an ice-bath 1.0 g (14.4 mmol) of hydroxylamine hydrochloride and 10 ml of pyridine are added to the suspension. The reaction mixture is stirred for 3 h at 0°C and subsequently diluted with water and an additional volume of methylene chloride. The aqueous layer is separated and extracted twice with 120 ml of methylene chloride containing 5 % of methanol. The organic phase is washed twice with water, dried over anhydrous sodium sulphate and concentrated in vacuo on a rotatory evaporator. The residue is recrystallized from methylene chloride yielding 4.11 g (96.5 %) of pale yellow crystals with a decoposition point of about 300 °C.

Example 8: 3'-demethyl-4'-demethylamino-4'-oxo staurosporine

0.25 g (0.55 mmol) of 3'-demethyl-4'-demethylamino-4' hydroximino staurosporine is added to 10 ml of dried dioxane. After addition of 0.1 ml of deionized water the reaction mixture is slightly warmed until a clear solution is obtained. Under stirring 168 µl (96%) of sulphuric acid is added. The reaction mixture is warmed to 60°C and stirred during one hour. The reaction mixture is subsequently diluted with 10 ml of methylene chloride and an additional volume of water. The organic solution is washed with 2 portions of 15 ml of ca. 0.5 N sodium hydrogencarbonate solution. The aqueous phase is reextracted with a small amount of methylene chloride. The combined organic extracts are washed with brine (saturated sodium chloride solution) and evaporated to dryness. The residue of ca. 0.22 g is purified by column chromatography on silica gel (LiChroprep Si 60, 15-25 µm, column diameter 2.0 cm; length 30 cm). The fractions eluted with methylene chloride containing 1 % of 2-

propanol are assayed by TLC. 0.133 g (55 %) of the compound is recovered as an amphoteric solid.

Example 9: O-carboxymethyl-4'-demethylamino-4'-hydroximino staurosporine

A solution of 0.12 g of 4'-demethylamino-4'-oxo staurosporine and O-(carboxymethyl)-hydroxylamine hemihydrochloride (0.995 g) in 24 ml ethanol and 120 µl pyridine is stirred during 20 hours. The reaction mixture is poured into 1% aqueous HCl and extracted twice with ethyl acetate. The organic solution is dried with a silicon-treated filter paper and the solvent removed *in vacuo*. The residue of 0.14 g is purified by preparative HPLC (Nucleosil 100-5 C_{18}, 16 x 250 mm, 290 nm, 8 ml/ Min.; solvent A: aqueous 0.1% TFA, solvent B: acetonitrile - H_2O - TFA : 80:20:0.08; isocratic elution at 80% solvent B) yielding 87 mg of O-carboxymethyl-4'-demethylamino-4'-hydroximino staurosporine as a colorless solid with MP >310 °C after lyophilization.

Example 10: O-acetyl-4'-demethylamino-4'-hydroximino staurosporine

A suspension of 466 mg (1.0 mmol) of 4'-demethylamino-4'-hydroximino staurosporine (TAN-1030A) in 5 ml of acetic anhydride, 3 ml of pyridine and 5 ml of methylene chloride is stirred at room temperature for 2 h. The mixture is diluted with 40 ml of methylene chloride, washed with 50 ml of a saturated aqueous solution of sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated *in vacuo*. Crystallisation from ethanol/ethyl acetate (75:25) yielded 480 mg (96 %) of pale yellow crystals with MP of 278 °C.

Example 11 : O-methylsulfo-4'-demethylamino-4'-hydroximino staurosporine

An ice-cooled mixture of 154 mg (0.33 mmol) of 4'-demethylamino-4'-hydroximino staurosporine (TAN-1030A), 9 ml of methylene chloride and 140 µl of triethylamine is treated with 52 µl (0.67 mmol) of methane sulfonic acid chloride. After stirring at 0°C for 10 min the mixture is evaporated in vacuum and the residue is subjected to silica gel column chromatography [methylene chloride/isopropanol (95:5)] affording 127 mg (71 %) as pale yellow crystals with MP of > 310 °C.

Example 12 : O,3'-diacetyl-3'-demethyl-4'-demethylamino-4'-hydroximino staurosporine

A suspension of 150 mg (0.33 mmol) of 3'-demethyl-4'-demethylamino-4' hydroximino staurosporine (example 7) in 1 ml of acetic anhydride and 2 ml of pyridine is stirred at room

temperature for 6 h. The mixture is diluted with 20 ml of methylene chloride, washed with 20 ml of a saturated aqueous solution of sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated in vacuum. The residue is purified by silica gel column chromatography [methylene chloride/isopropanol (95:5)] to obtain 159 mg (89 %) O,3'-diacetyl-3'-demethyl-4'-demethylamino-4'-hydroximino staurosporine as pale yellow crystals with MP of 288-292 °C.

Table 1: ^{1}H-NMR chemical shifts in DMSO-d_6 recorded at ambident temperature. The numbering follows that of staurosporine [a) in CD_2Cl_2].

The capital letters A to H in row 1 stand for the following compounds:
A is 4'-demethylamino-4'-oxo staurosporine according Example 1
B is O-methyl-4'-demethylamino-4'-hydroximino staurosporine according Example 5
C is O-benzyl-4'-demethylamino-4'-hydroximino staurosporine according Example 6
D is 3'-demethyl-4'-demethylamino-4' hydroximino staurosporine according Example 7
E is 3'-demethyl-4'-demethylamino-4'-oxo staurosporine according Example 8
F is O-acetyl-4'-demethylamino-4'-hydroximino staurosporine according Example 10
G is O-methylsulfo-4'-demethylamino-4'-hydroximino staurosporine according Example 11
H is O,3'-diacetyl-3'-demethyl-4'-demethylamino-4'-hydroximino staurosporine according Example 12

Table 1:

Compound	A	B [a)]	C	D	E [a)]	F [a)]	G	H [a)]
Example	1	5	6	7	8	10	11	12
1	7.72 (d)	7.4*	7.71	7.71	7.41	7.42	7.80	7.42
2	7.53 (t)	7.54	7.48	7.52	7.56	7.56	7.53	7.56
3	7.35 (t)	7.36*	7.29	7.29	7.35	7.38	7.37	7.38
4	9.31 (d)	9.38	9.35	9.32	9.35	9.39	9.32	9.40
6	8.62 (s)	6.41	8.63	8.40	6.38	6.33	8.61	6.51
7	4.98 (s)	5.00	4.99 4.92	4.96	5.93 4.96	5.03	4.96	5.05 4.96
8	7.99 (d)	7.93	7.95	7.98	7.92	7.94	8.05	7.84
9	7.35 (t)	7.42*	7.33	7.33	7.38	7.41	7.33	7.41

Compound	A	B [a)]	C	D	E [a)]	F [a)]	G	H [a)]
10	7.47 (t)	7.47	7.41	7.45	7.50	7.50	7.48	7.53
11	8.02 (d)	7.98	7.96	8.12	8.14	7.97	8.02	7.98
3'	5.08 (s)	4.47	4.84	5.41	5.06	4.59	5.13	5.98
5'a	3.99 (dd)	2.92	3.11	3.04	3.09	3.09	3.42	3.17
5'b	2.67 (d)	3.80	3.69	3.63	3.74	3.85	3.53	3.89
6'	7.44 (d)	6.80	7.10	7.04	7.23	6.87	7.22	6.92
2'-CH_3	2.57 (s)	2.55	2.48	2.48	2.63	2.60	2.02	1.92*
3'-OCH_3	3.42 (s)	3.53*	3.40			3.53	3.47	
3'-OH				4.96	3.65			
4' =NOH				10.32				
OCH_3		3.20*						
p-C_6H_5			6.98					
m-C_6H_5			6.85					
o-C_6H_5			6.23					
o-CH_2-C_6H_5			4.53 4.28					
SO_2CH_3							2.58	
CH_3CO						1.45		2.62* 1.43*

Example 13: Tablets each comprising 20 mg of active ingredient (e.g. 3'-demethyl-4'-demethylamino-4'-oxo staurosporine) are prepared in the customary manner, for example in the following composition:

Composition:

active ingredient	20 mg
wheat starch	60 mg
lactose	50 mg
colloidal silica	5 mg
talc	9 mg
magnesium stearate	1 mg
	145 mg

Preparation:

The active ingredient is mixed with a portion of the wheat starch, with lactose and colloidal silica and the mixture is forced through a sieve. A further portion of the wheat starch is made into a paste with 5 times the amount of water on a water bath and the powder mixture is kneaded with the paste until a slightly plastic mass is obtained.

The plastic mass is pressed through a sieve of about 3 mm mesh size and dried, and the resulting dry granules are forced through a sieve once more. Then, the remainder of the wheat starch, the talc and the magnesium stearate are admixed and the mixture is pressed to form tablets each weighing 145 mg and having a breaking notch.

Example 14: Tablets each comprising 1mg of active ingredient (e.g. 3'-demethyl-4'-demethylamino-4'-hydroximino staurosporine) are prepared in the customary manner in the following composition:

Composition:

active ingredient	1 mg
wheat starch	60 mg
lactose	50 mg
colloidal silica	5 mg
talc	9 mg
magnesium stearate	1 mg
	126 mg

Preparation:

The active ingredient is mixed with a portion of the wheat starch, with lactose and colloidal silica and the mixture is forced through a sieve. A further portion of the wheat starch is made into a paste with 5 times the amount of water on a water bath and the powder mixture is kneaded with the paste until a slightly plastic mass is obtained.

The plastic mass is pressed through a sieve of about 3 mm mesh size and dried, and the resulting dry granules are forced through a sieve once more. Then, the remainder of the wheat starch, the talc and the magnesium stearate are admixed and the mixture is pressed to form tablets each weighing 126 mg and having a breaking notch.

Example 15: Capsules each comprising 10mg of active ingredient (3'-demethyl-4'-demethylamino-4'-oxo staurosporine) are prepared in the customary manner as follows:

Composition:

active ingredient	2500 mg
talc	200 mg
colloidal silica	50 mg

Preparation:

The active ingredient is homogeneously mixed with talc and colloidal silica, and the mixture is forced through a sieve of 0.5 mm mesh size and introduced in portions of 11 mg into hard gelatine capsules of a suitable size.

Example 16: Capsules, each comprising 25 mg of active ingredient, for example one of the compounds of the formula I described in the preceding examples, are prepared as follows:

Composition

active ingredient

gelucire 44/14

(gelucire 44/14 is admixture of esters of saturated C_8-C_{18}-fatty acids with glycerol and polyethylene glycol having a molecular weight of approximately 1500; produced by Gattefossé, F-69800 Saint Priest, France).

Preparation

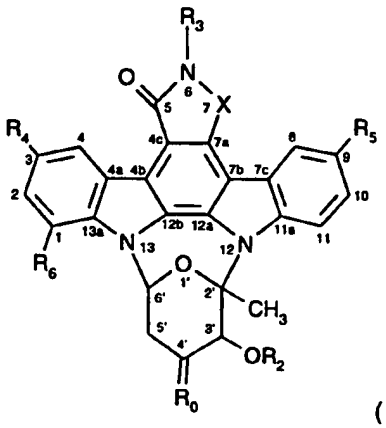
A portion of gelucire 44/14 is melted at a temperature of from 50°C to 100°C. The active ingredient is mixed with the liquid gelucire 44/14 in a heated mortar to form a paste. The remainder of the gelucire 44/14 is then also melted and is added to the paste. The mixture is stirred at 50°C until a solution is obtained. This is introduced into the capsules while warm and is cooled. The wax so obtained comprises 12 % by weight active ingredient.

The wax-like dispersion can also be processed in water by ultrasound treatment to form a milky liquid that can be administered orally.

Example 17: It is also possible to prepare pharmaceutical compositions comprising as active ingredient another of the compounds of formula I described in Examples 1 to 12 instead of the compositions described in Examples 13 to 16.

What is claimed is:

1. A compound of the formula I



(I),

wherein X is methylene, carbonyl or hydroxymethylene, R_0 is oxygen or N-OR_1, R_1 is hydrogen, alkyl, cycloalkyl, aralkyl, acyl, SO_2-R_a, or carboxyalkyl; R_a is lower alkyl, cycloalkyl; R_2 is hydrogen, lower alkyl, cycloalkyl or acyl, R_3 is hydrogen, halogen, amino, acyl, alkyl, cycloalkyl, alkoxyalkyl or aralkyl, R_4 and R_5 independent of each other are hydrogen, hydroxy, nitro, amino, lower alkyl, cycloalkyl, lower alkoxy, carbamoyl or halogen, and R_6 is hydrogen or nitro, excluding the compound wherein X is methylene, R_0 is N-OH, R_2 is methyl and R_3, R_4, R_5 and R_6 are hydrogen, and salts thereof.

2. A compound of formula I according to claim 1, wherein X is methylene, carbonyl or hydroxymethylene, R_1 is hydrogen, acyl of the partial formula Z-C(=W)-, wherein W is oxygen or sulfur and Z is C_1-C_7alkyl which is unsubstituted or substituted by phenyl, phenyloxy, carboxy, cyano, C_1-C_4alkoxycarbonyl, amino and/or by halogen, phenyl which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4 alkoxycarbonyl, methylenedioxy and/or by cyano, C_1-C_{20}alkoxy, phenyloxy or benzyloxy each of which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano,acyl of the partial formula (R_7)(R_8)N-C(=W)-, wherein W is sulfur or oxygen, R_7 is hydrogen and R_8 is C_1-C_7alkyl or phenyl each of which is unsubstituted or substituted by C_1-C_4 alkyl, C_1-C_4-

alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano, or is an acyl radical derived from an α-amino acid selected from glycine, phenylglycine, alanine, phenylalanine, proline, leucine, isoleucine, serine, threonine, valine, tyrosine, arginine, histidine, lysine, glutamine, glutamic acid, aspartic acid and asparagine, in which the α-amino group is free or protected by an amino-protecting group and it being possible, in corresponding amino acids having an additional carboxy group, for the carboxy group also to be esterified, or wherein R_1 is C_1-C_7alkyl, C_2-C_7hydroxyalkyl in which the hydroxy group is in any position other than the 1-position, cyano-[C_1-C_7]alkyl or carboxy-[C_1-C_7]alkyl in which the carboxy group is in the form of a C_1-C_4alkyl ester or a benzyl ester, R_2 is carboxy, alkoxycarbonyl, carbamoyl, cyano or esterified carboxy that can be cleaved under physiological conditions, and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

3. A compound of formula I according to claim 1, wherein X is methylene, carbonyl or hydroxymethylene, $R_1$is hydrogen, acyl of the partial formula Z-C(=O)-, wherein Z is C_1-C_7-alkyl which is unsubstituted or substituted by phenyl, phenyloxy, halogen, carboxy and/or by C_1-C_4 alkoxycarbonyl, or phenyl, C_1-C_7alkoxy or phenyloxy each of which is unsubstituted or is substituted by halogen, carboxy, C_1-C_4alkoxycarbonyl, C_1-C_4alkoxy, C_1-C_4alkyl and/or by nitro, or the acyl radical of a naturally occurring α-amino acid selected from glycine, alanine, serine and phenylalanine in which the amino group may be protected by an amino-protecting group, or wherein R_1 is C_1-C_4alkyl, cyano-C_1-C_4alkyl or carboxy- C_1-C_4alkyl, R_2 is carboxy or C_1-C_7alkoxycarbonyl, and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

4. A compound of formula I according to claim 1, wherein X is methylene, carbonyl or hydroxymethylene, R_1 is hydrogen, benzoyl, C_1-C_4alkoxycarbonyl, or glycyl or L-alanyl in each of which the amino group may be protected by C_1-C_4alkoxycarbonyl, R_2 is carboxy or C_1-C_4 alkoxycarbonyl and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

5. A compound of the formula I according to any one of claims 1 to 4, wherein R_3, R_4, R_5, and R_6 are hydrogen; or a salt thereof.

6. A compound of the formula I according to any one of claims 1 to 4, wherein R_3, R_4, R_5, and R_6 are hydrogen, and X, R_0 and R_2 are defined as under formula I or as in any one of the preceding subgroups; or a salt thereof.

7. A compound of the formula I according to any one of claims 1 to 4, wherein X stands for methylen, R_3, R_4, R_5, and R_6 are hydrogen, and R_0 and R_2 are defined as under formula I or as in any one of the preceding subgroups; or a salt thereof.

8. A compound of the formula I according to any one of claims 1 to 4, wherein X stands for carbonyl, R_3, R_4, R_5, and R_6 are hydrogen, and R_0 and R_2 are defined as under formula I or as in any one of the preceding subgroups; or a salt thereof.

9. A pharmaceutically acceptable salt of a compound of formula I according to any one of claims 1 to 8.

10. A compound of the formula I according to claim1 or a pharmaceutically acceptable salt thereof, selected from the group of compounds consisting of:
4'-demethylamino-4'-oxo staurosporine,
O-methyl-4-demethylamino-4'-hydroximino staurosporine,
O-benzyl-4-demethylamino-4'-hydroximino staurosporine,
3'-demethyl-4'-demethylamino-4' hydroximino staurosporine,
3'-demethyl-4'-demethylamino-4'-oxo staurosporine,
O-carboxymethyl-4'-demethylamino-4'-hydroximino staurosporine,
O-acetyl-4'-demethylamino-4'-hydroximino staurosporine,
O-methylsulfo-4'-demethylamino-4'-hydroximino staurosporine, and
O,3'diacetyl-3'-demethyl-4'-demethylamino-4'-hydroximino staurosporine.

11. A pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 10 together with a pharmaceutical carrier.

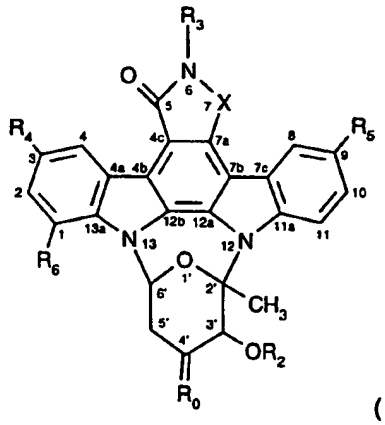
12. A compound of formula I or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 10 for use in a method for the therapeutic treatment of the human or animal body.

13. The use of a compound of formula I according to any one of claims 1 to 10 for the preparation of a pharmaceutical composition to be used for the inhibition of protein kinase C.

14. A method for the treatment of warm-blooded animals, including humans, suffering from abnormally increased cell proliferation, wherein a compound of formula I or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 10 is administered to such a warm-blooded animal at a dosage that retards said cell proliferation.

15. A method of suppressing the immune system of warm-blooded animals comprising administering to a warm-blooded animal in need of such treatment an immunosuppressing effective amount of a compound of the formula I or of a pharmaceutically acceptable salt thereof according to any one of claims 1 to 10.

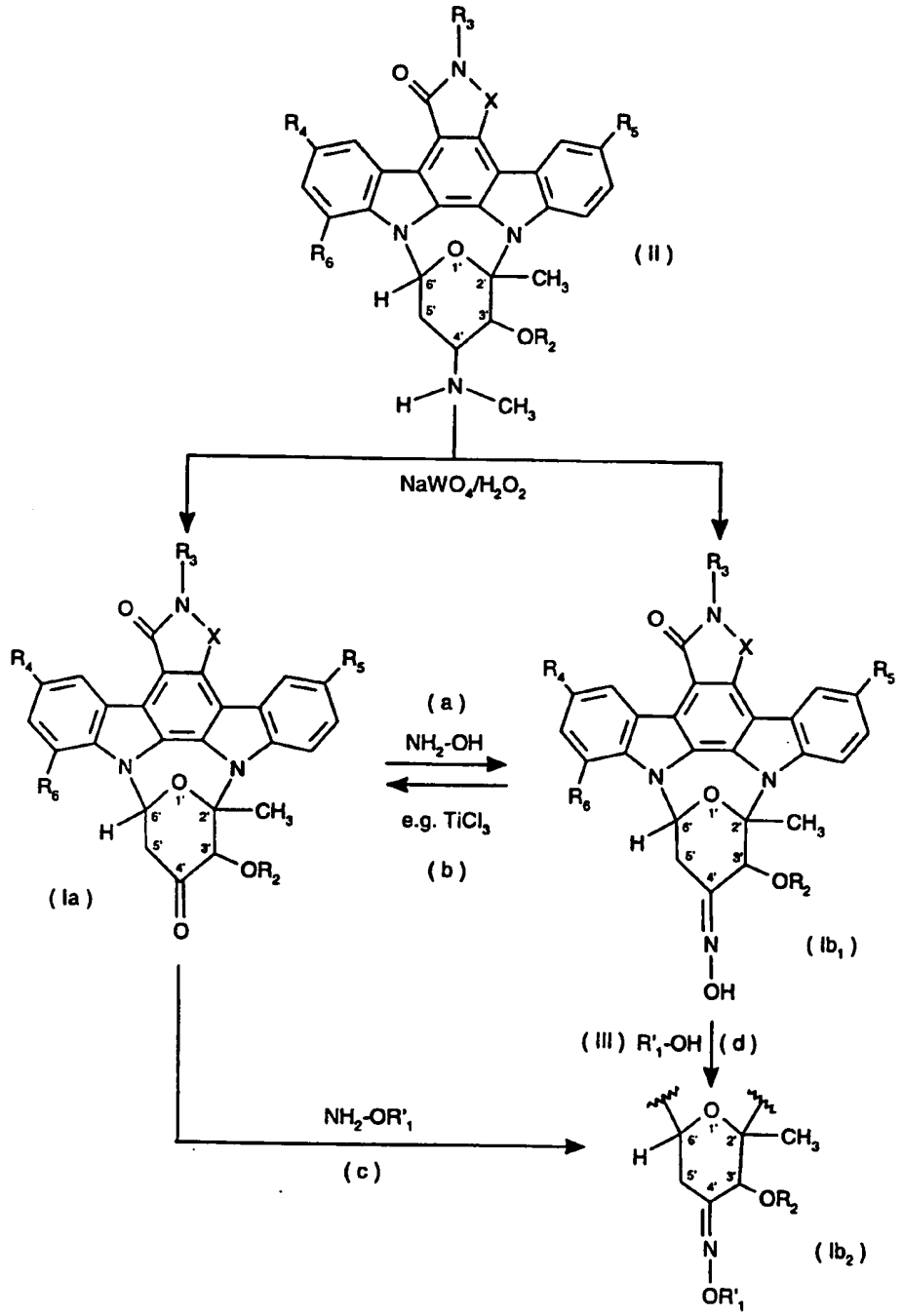
16. A process for the preparation of a compound of formula I



(I),

wherein X is methylene, carbonyl or hydroxymethylene, R_0 is oxygen or N-OR_1, R_1 is hydrogen, alkyl, cycloalkyl, aralkyl, acyl, SO_2-R_a, or carboxyalkyl; R_a is lower alkyl or cycloalkyl; R_2 is hydrogen, lower alkyl, cycloalkyl or acyl, R_3 is hydrogen, halogen, amino, acyl, alkyl, cycloalkyl, alkoxyalkyl or aralkyl, R_4 and R_5 independent of each other are hydrogen, hydroxy, nitro, amino, lower alkyl, cycloalkyl, lower alkoxy, carbamoyl or halogen,

and R_6 is hydrogen or nitro, and salts thereof, said process being carried out in accordance with the following reaction scheme



wherein the substituents X, R_2, R_3, R_4, R_5 and R_6 are defined as above and R'_1 is one of the radicals R_1 with the exception of hydrogen,
and which process comprises
oxidising a compound of the formula II with a suitable oxidising agent, e.g. $NaWO_4/H_2O_2$, to result in a mixture of a ketone of the formula Ia and an oxime of the formula Ib_1, isolating the mixture and separating the keton Ia from the oxime Ib_1 and
(a) optionally derivatizing the ketone Ia with a suitable derivatizing agent, e.g. NH_2-OH, to form the oxime Ib_1 or
(b) optionally hydrolyzing the oxime Ib_1 with a suitable hydrolyzing agent, e.g. $TiCl_3$, to form a ketone Ia or
(c) optionally derivatizing the ketone Ia with a derivatizing agent NH_2-OR'_1, wherein R'_1 is one of the radicals R_1 with the exception of hydrogen, to form the oxime Ib_2, wherein R'_1 has the same meanings or
(d) optionally derivatizing the oxime Ib_1 with a suitable alkylation or acylation reagent R'_1 - OH, to form the oxime Ib_2, wherein R'_1 is alkyl, cycloalkyl, aralkyl, acyl, SO_2-R_a, or carboxyalkyl and R_a is lower alkyl or cycloalkyl,
(e) optionally derivatizing R_2 standing for hydrogen with an alkylating or acylating agent, and converting a compound of formula Ia, Ib_1 or Ib_2 obtained in free form into a salt thereof or a compound of formula Ia, Ib_1 or Ib_2 obtained in the form of a salt into its free form or into a different salt.

17. A process according to claim 16 wherein the oxidising agent is sodium tungstate dihydrate and H_2O_2.

18. A process according to claim 16 wherein the agent according to step (c) for derivatizing ketones of the formula Ia to oximes of the formula Ib is NH_2-OR'_1, wherein R'_1 stands for alkyl, aralkyl, acyl, SO_2-R_a, or carboxyalkyl; wherein R_a is lower alkyl.

19. A compound obtainable by the process according to claim 16.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/[redacted]96/03164

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D498/22 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 113, no. 5, 30 July 1990 Columbus, Ohio, US; abstract no. 38898p, XP002018019 see abstract & JP,A,01 246 288 (TAKEDA CHEMICAL INDUSTRIES, LTD.) ---	1-13, 16-19
Y	TETRAHEDRON, (INCL TETRAHEDRON REPORTS), vol. 47, no. 22, 1991, OXFORD GB, pages 3565-3574, XP002018018 S. TSUBOTANI ET AL.: see page 3565 ---	1-13, 16-19
Y	EP,A,0 643 966 (KYOWA HAKKO KOGYO KABUSHIKI KAISHA) 22 March 1995 see abstract; claim 1 ---	1-13, 16-19
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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 November 1996	27.11.96

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Week 9526 Derwent Publications Ltd., London, GB; AN 95-196729 XP002018020 & JP,A,07 112 987 (ASAHI KASEI KOGYO KK) , 2 May 1995 see abstract	1-13, 16-19
Y	DATABASE WPI Week 9327 Derwent Publications Ltd., London, GB; AN 93-216794 XP002018021 & JP,A,05 140 168 (ASAHI CHEM. IND. CO., LTD.) , 8 June 1993 see abstract	1-13, 16-19
Y	WO,A,95 07911 (CEPHALON, INC.) 23 March 1995 see abstract; claim 1	1-13, 16-19

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INTERNATIONAL SEARCH REPORT

Int. [redacted] pplication No
PCT/[redacted]96/03164

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WO-A-9507911	23-03-95	US-A-	5468872	21-11-95
		AU-A-	7836394	03-04-95
		CA-A-	2171561	23-03-95
		EP-A-	0719268	03-07-96
		FI-A-	961236	15-03-96
		NO-A-	961087	13-05-96
		US-A-	5516772	14-05-96

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